REMARKS

Applicants thank the Examiner and her supervisor for the courtesy of the in person interview extended to the Applicants' undersigned representative and Dr. Richard Fox on Friday, November 13, 2009. During the interview the concept of a sequence activity model was discussed and distinguished from the Hellberg and Schellenberger references. To draw the distinction more clearly, Applicants' representative offered to amend the claims to recite that the sequence active model employs independent variables specifying the presence or absence of nucleotides at corresponding positions in a sequence. The Examiners indicated that they would be favorably disposed toward such amendments.

Claims 76-81, 102-108, and 120-125 are pending in the application and stand rejected. Claim 101 has been cancelled. New claims 123-125 have been added. These claims parallel previously added claims 120-122.

Claims 76, 79, 102-105, 108, and 120 have been amended. At the Examiner's request, claims 76, 79, and 120 have been amended to delete the words "computational algorithmic". Additionally, dependent claims 102-105 have been amended to update their dependency in light of cancellation of claim 101.

Independent claim 76 has been amended to recite that the sequence activity model is for predicting "activity as a function of independent variables specifying the presence or absence of nucleotides at ~~nucleotide types and~~ corresponding ~~position~~ positions in the nucleotide sequence". Independent claim 79 has been similarly amended. Support for these amendments is found at, for example, the bottom of page 25.

Further, independent claim 79, which is a computer program product claim, has been amended to recite that the computer readable medium is a "computer readable *storage* medium". Support for this amendment is found for example in a section of the specification beginning at page 80.

The Provisional Double Patenting Rejection

Claims 76-81 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-9, and 14 of copending Application No. 11/706,034 in view of Hellberg et al. Applicants will consider this rejection again when an indication of allowable subject matter is made in either the present application or Application No. 11/706,034 (Attorney Docket MXGNP004X2D1). Applicants note that Application No. 11/706,034 was filed after the present application.

The Rejection under 35 USC 103(a)

Claims 76-81 and 101-108, and 120-122 were rejected under 35 USC 103(a) as being unpatentable over Hellberg et al. (J. Med. Chem., vol. 30 (1987) pgs. 1126-1135) in view of Schellenberger et al. (US Patent Pub. No. 2002/0155460). Applicants respectfully traverse these rejections and submit that the cited references fail to teach all elements of the rejected claims. Withdrawal of the rejections is respectfully requested.

As explained during the interview, the independent claims recite a *sequence activity model* relating activity to nucleotides and their corresponding positions in a sequence. The prior art does not show or suggest this. As explained, Hellberg and related references employ a traditional QSAR approach which constructs a model from independent variables representing quantitative physico-chemical information about amino acids. In the case of Hellberg, the independent variables are the "z-scale" parameters described at page 1127. Each amino acid is described by the numerical values for 3 different z-scales as shown in Table II. These parameters are constructed from 29 different physico-chemical properties including molecular weight, various equilibrium constants, NMR spectral information, partition coefficients, HPLC retention times, etc. See Table I on page 1127. Hellberg's approach should be contrasted with the claimed invention, which employs the presence or absence of nucleotides in a sequence activity model. As agreed to in the interview, Applicants have amended the independent claims to more clearly emphasize the differences between the independent variables of Hellberg and those of the claimed invention. To this end, the claims have been amended to recite "independent variables specifying the presence or absence of nucleotides at corresponding positions in the nucleotide sequence".

As explained during the interview, the recited sequence activity models (those employing independent variables specifying the presence or absence of nucleotides) provide various advantages over traditional QSAR models such as those employed by Hellberg. For example, the sequence activity models employed in the claimed invention make it easier to decipher the effects of substitutions in a nucleotide sequence. An improvement in activity may be attributed directly to the presence (or absence) of a nucleotide at a particular sequence position. With Hellberg's model, changes in activity can be attributed only to a combination of physical properties (as is the case with Hellberg's models), which properties may be shared by many different amino acids to varying degrees. Additionally, employing independent variables specifying the presence or absence of nucleotides permits one to produce useful models with relatively little data (i.e., using smaller training sets) than is possible with the Hellberg approach.

It is also worth noting that Hellberg's model is limited to amino acid sequences, hence the physical properties comprising the independent variables relate only to amino acids. Given the context of Hellberg's model development, it is improper to extrapolate from Hellberg's peptide models to the nucleotide sequence models recited in the claims.

The limitations of Schellenberger have been detailed in responses to previous office actions. The reference fails to suggest a sequence activity model of the type recited in the claims. It proposes a method employing probabilities that certain individual residues will impact desired characteristics of biological molecules. The overall method includes: generating a *probability matrix*, setting a *constraint vector*, designing a substitution scheme based on the matrix and the vector, constructing a library based on the scheme, and finally characterizing the members of the library (see paragraph [0012]).

Specifically, Schellenberger's probability matrix contains probability estimates that "a given residue" will impact a desired activity in a biological polymer (see paragraph [0059], also cited in the Office Action in §9 on page 11). It does not allow prediction of activity. FIG. 1 illustrates an example of the matrix, where each row represents a residue position in a biological polymer and each column represents one type of residue (see paragraph [0060]). The matrix shows a probability estimate at the intersection of each row and column, illustrated as a vertical bar in FIG. 1. This estimate represents the probability that a polymer will have a desired activity if that particular residue (column value) is found in that position (row value) (see paragraph [0060]). It does not allow for predicting activity. Thus Schellenberger's approach falls well short of a sequence activity model that estimates activity for a sequence. Unlike a sequence activity model, Schellenberger's probability matrix simply considers the probability of a single residue at a single position and ignores other aspects of a sequence that collectively impact the activity of the sequence. Therefore, the probability matrix is not representative of a computational algorithmic sequence activity model.

As indicated, Schellenberger's method employs a constraint vector, which is applied to the probability matrix in order to select mutations to be included in the library. Schellenberger provides a few examples of constraint vectors: a correlation matrix (see [0073], a proximity-based method (see [0074] – [0078]), correlation in evolutionary data (see [0078]) and conservation indexes (see [0079]). FIG. 1 illustrates application of the constraint vector to the matrix. The reference indicates that the candidates for mutagenesis are only those positions in the matrix that have probability values higher than the corresponding values in the constraint vector. Essentially, the vector acts as a set of thresholds that provides minimum desired probabilities for each residue in each position. Applying the vector to the matrix simply limits the number of residues and positions for mutagenesis in order to generate "a library of a size which can be effectively screened for a desire property" (see paragraphs [0082]). The constraint

vector and the process of applying the vector to the matrix are not representative of a sequence activity model.

In view of the above, Applicants respectfully request that the art rejections be withdrawn.

Applicants also wish to point out that claim 76 recites

> using the sequence activity model to rank positions in a reference nucleotide sequence and/or nucleotide types at specific positions in the reference nucleotide sequence in order of impact on the desired activity

The Office Action points to Hellberg's Table V and page 1129, col. 2, lines 33-40 as teaching this element of the claim (see ¶s 5 and 6 on pages 6 and 7 of the Office Action). The cited portions of Hellberg pertain to selection of sequences for use in developing a model. In other words, the cited portions pertain to identification of those sequences that may serve as members of a training set. The cited portions have nothing to do with *using* the model to rank positions or nucleotide types in nucleotide sequence. Because a model does not yet exist when applying the cited portion of Hellberg, a model cannot be employed to rank nucleotide sequence positions or nucleotide types as claimed. Applicants therefore respectfully submit that Hellberg does not teach the recited element of claims 76.

More specifically, Hellberg's Table V illustrates a fractional factorial design matrix with four positions and sixteen possible combinations resulting from varying values of the positions. The positions are identified to select peptides used to develop a model. On page 1129, col. 2, "Design Example" section, Hellberg describes a process of generating and using such matrix. The process is designed to select only the most informative samples from all available analogous. The disclosed technique simply shows a tool for selecting members of a training set to be used in developing a model.

For the above reasons, claim 76 is patentable over the cited art. Claims 77, 78, 102-108, and 120-122 are dependent from claim 76 and are therefore likewise patentable over the cited art. Claims 79-81 and 123-125 are patentable over the cited art for similar reasons. Withdrawal of all art rejections is respectfully requested.

Conclusion

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a

telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

If any fees are due in connection with the filing this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 504480 (Order No. MXGNP004X1).

Respectfully submitted,
WEAVER AUSTIN VILLENEUVE & SAMPSON LLP

/ Jeffrey K. Weaver/
Jeffrey K. Weaver
Registration No. 31,314

510-663-1100
P.O. Box 70250
Oakland, CA 94612-0250